

# Comparative efficacy of intravenous dexmedetomidine, clonidine, and tramadol in postanesthesia shivering

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## Abstract

**Background and Aims:** Postanesthesia shivering continues to be a major challenge in the perioperative care. We compared the efficacy of tramadol, clonidine, and dexmedetomidine in preventing postoperative shivering and its potential adverse effects in patients undergoing laparoscopic cholecystectomy under general anesthesia.

**Material and Methods:** One hundred and twenty American Society of Anesthesiologists I and II patients scheduled for elective laparoscopic cholecystectomy under general anesthesia were divided into four equal groups. Group 1 received clonidine 2 µg/kg, Group 2 received tramadol 1 mg/kg, Group 3 received dexmedetomidine 1 mcg/kg all intravenous diluted in NS to 5 ml, and Group 4 received NS intravenous 5 ml. Parameters analysed included postoperative blood pressure (BP), pulse rate, respiratory rate (RR), arterial saturation, and tympanic membrane temperature. Patients were observed for shivering episodes, sedation, pain, respiratory depression, nausea, and vomiting. Analysis of variance, Tukey's *post-hoc* comparison, Chi-square test and Bonferroni *post-hoc* comparison test were performed using SPSS (Statistical analysis by Statistical Package of Social Sciences of Microsoft Windows) Statistics (version 16.0).

**Results:** The incidence of shivering was 10, 3.3, 13.3 and 40% in Groups 1, 2, 3, and 4 respectively. Patients who were given tramadol had significantly less shivering than patients in clonidine and dexmedetomidine groups ( $P < 0.01$ ).

**Conclusion:** All the three drugs were effective in preventing postoperative shivering. However, tramadol has been found to be more efficacious in preventing postoperative shivering.

**Key words:** Clonidine, dexmedetomidine, general anesthesia, postanesthesia shivering, tramadol

## Introduction

The reported incidence of shivering following general anesthesia is 5-65% and 33% in patients following regional anesthesia. Peri-operative hypothermia, a major cause of postanesthesia shivering has been associated with adverse outcomes including sympathetic nervous system stimulation, metabolic acidosis, prolonged drug metabolism delayed recovery, decreased platelet activity, and impaired immune responses.<sup>[1]</sup>

Prevention of postanesthesia shivering, improves the outcome in terms of reduced morbidity and blood loss, improved wound healing, and shorter hospital stay. Numerous drugs such as tramadol,  $\alpha_2$  agonists, opiates, ketanserin,  $MgSO_4$ , steroids, 6HT<sub>3</sub> antagonists have been proposed for the treatment of postoperative shivering. A thorough literature research revealed that individually tramadol, clonidine,<sup>[2]</sup> and dexmedetomidine<sup>[3]</sup> have been proven to be efficacious for the treatment of postoperative shivering,<sup>[4]</sup> but a comparative randomized trial for efficacy has not been undertaken.

Hence we aimed to compare tramadol, clonidine, and

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dexmedetomidine for prevention of postanesthesia shivering.

## Material and Methods

After obtaining approval from the Institutional Ethical Committee and written informed consent, a randomized double-blind study was conducted on 120 adult American Society of Anesthesiologists status I & II patients of either sex, scheduled for elective laparoscopic cholecystectomy under general anesthesia. Morbidly obese (BMI >30 kg/m<sup>2</sup>), patients with coexisting diseases such as IHD, hepatic, renal insufficiency, patients with neuromuscular and psychiatric disturbances, body temperature below 35°C during operation, preoperative febrile condition, hypothyroidism, hyperthyroidism, patients on vasodilator medication and those requiring laparotomy during surgery were excluded from study.

The patients were randomly assigned to four groups of 30 patients each using computer generated random number list.

- Group 1: Clonidine 2 µg/kg intravenous diluted in normal saline (NS) to 5 ml.
- Group 2: Tramadol 1 mg/kg intravenous diluted in NS to 5 ml.
- Group 3: Dexmedetomidine 1 mcg/kg intravenous diluted in NS to 5 ml.
- Group 4: NS intravenous 5 ml.

Patients were informed about the visual analog scale (VAS) [5] preoperatively. On arrival in the operating room, baseline heart rate (HR), BP, RR, SpO<sub>2</sub>, and body temperature (axillary, tympanic membrane temperature) were recorded. A large bore intravenous cannula was inserted. Operating room temperature was maintained at 22°C.

All patients were administered injection glycopyrrolate 0.2 mg, metoclopramide 10 mg and fentanyl 1 µg/kg over a period of 5 min before induction of anesthesia. Propofol 1% was titrated to loss of verbal response. Tracheal intubation was facilitated using inj. succinylcholine chloride 2m/kg as a bolus dose. A loading dose of inj. atracurium 0.5 mg/kg was given after confirming the correct position of the tracheal tube using EtCO<sub>2</sub> and presence of bilateral equal air entry on auscultation. Anesthesia was maintained with N<sub>2</sub>O:O<sub>2</sub> 6:3, intravenous infusion of propofol at 50-150 µg/kg/min and repeated doses of atracurium 0.1 mg/kg given every 15-20 min. Injection fentanyl 0.5 µg/kg was repeated after 1 h intra-operatively. All patients were covered by surgical drapes throughout the surgery and no active warming was done. Vitals were recorded after

every 5 min for the 1<sup>st</sup> h followed by every 10 min for next 2 h. Core temperature was recorded by infrared tympanic membrane thermometer before induction, immediately after induction of anesthesia, thereafter every 30 min until the completion of surgery.

At the beginning of wound closure, the test drug (prepared by a person not involved in the study), was administered intravenously over a period of 5 minutes using a syringe pump. All observations were recorded by a blinded observer.

At the end of anesthesia, the neuromuscular blockade was antagonized with injection neostigmine 0.04 mg/kg and injection glycopyrrolate 0.02 mg/kg intravenously. Trachea was extubated when respiration was adequate and patient was able to obey verbal commands.

Postoperatively, the patients received O<sub>2</sub> via venturi mask and were covered with a single cotton blanket. HR, noninvasive blood pressure, SpO<sub>2</sub>, and tympanic membrane temperature were measured and recorded on admission to recovery room (T<sub>0</sub>), 10 min (T<sub>10</sub>), 20 min (T<sub>20</sub>) and 30 min (T<sub>30</sub>) and then half hourly intervals for 4 h. Besides this, patients were observed for shivering episodes, sedation, pain, respiratory depression, nausea, and vomiting.

Shivering was graded using a five scale point scale.<sup>[6]</sup>

The pain was assessed by using 0-10 cm VAS where 0 — no pain and 10 — worst imaginable pain. Respiratory depression was defined as RR < 8 /min. The degree of sedation was graded according to Ramsay Sedation Score.<sup>[7]</sup>

If the core temperature fell below 35°C, active rewarming of the patient was initiated and a repeat dose of tramadol 50 mg was given. VAS score more than 3 was treated with injection diclofenac sodium 75 mg slow intravenously in 100 ml NS. The number of patients requiring rescue analgesics during 4 h study period and the time to rescue analgesia after extubation and total amount of analgesic required was noted.

## Statistical analysis

The results were tabulated and subjected to statistical analysis by Statistical Package of Social Sciences of Microsoft Windows (SPSS) version 16 (SPSS Inc., Chicago, IL, USA). Tests used were analysis of variance (ANOVA), Tukey's *post-hoc* comparison, Chi-square test and Bonferroni *post-hoc* comparison test.

## Results

The demographic data of all the four groups were comparable.

The mean duration of surgery showed no statistically significant difference ( $P = 0.861$ ) among the four groups of patients [Table 1].

Out of 120 patients included in the study, 16.7% had shivering. The number of patients experiencing shivering was maximum in Group 4 where 12 out of 30 (40%) patients shivered. On the other hand, 4 (13.3%), 3 (10%) and 1 (3.3%) patients shivered in Group 3, 1, and 2, respectively. This difference was highly significant with a  $P$  value of 0.007 after application of Chi-square test with Bonferroni correction. All test groups had significantly less shivering than the control group. The tramadol group (Group 2) had significantly less shivering than the clonidine (Group 1) or dexmedetomidine (Group 3) groups. There was no significant difference between Groups 1 and 3 [Figure 1].

The number of patients who experienced significant shivering requiring treatment (Grade  $\geq 2$ ) was greater in the control group (12 out of 30 patients) compared to the other groups. No patient in Group 1, 2, and 3 had Grade 3 shivering whereas three patients of Group 4 had Grade 3 shivering.

No difference was observed in core temperatures on admission to recovery room between patients who shivered and those who did not shiver in all the four study groups [Table 2].

The mean grade of sedation on admission to recovery room was  $2.4 \pm 0.5$  in Group 1,  $2.1 \pm 0.3$  in Group 2,  $2.3 \pm 0.5$  in Group 3 and  $2.1 \pm 0.3$  in Group 4. This difference was found highly significant ( $P = 0.001$ , ANOVA). Group 1 patients

had higher sedation scores than Group 2, 3, and 4 from the time of admission to recovery room until 60 min. No difference in sedation was observed in patients receiving tramadol (Group 2) when compared to (Group 4) and d (Group 3).

At the time of admission to recovery room the mean RR in Group 1 was  $15.8 \pm 3.0/\text{min}$ , Group 2 was  $15.1 \pm 1.5/\text{min}$ , Group 3  $14.4 \pm 1.8/\text{min}$  and Group 4  $15.4 \pm 2.6/\text{min}$ . From 0 to 240 min interval, there were no significant difference among all groups.

Pulse rate of patients at 0 min (on admission to recovery room), in Group 1 was  $73.4 \pm 9.4/\text{min}$ , Group 2 was  $83.5 \pm 13.4$ , Group 3 was  $64.1 \pm 7.1$  and Group 4 was  $89.2 \pm 9.9$ . This difference was statistically significant with  $P$  value of 0.0001 till 210 min and 0.003 at 240 min. The mean pulse rates of patients who received clonidine and dexmedetomidine were comparable, however, it did not require treatment.

Postoperative mean systolic BP (SBP) from the time of admission in the recovery room (0 min) to 240 min of all the four groups revealed statistically significant differences until 180 min after which differences were not significant. At 0 and 10 min the mean SBP of clonidine group ( $123.9 \pm 8.2$  mmHg) was significantly lower than tramadol group ( $137.4 \pm 13.8$  mmHg) and control group ( $142.3 \pm 9.8$ ) and the mean SBP of dexmedetomidine group ( $127.7 \pm 8.6$  mmHg) was also lower than the tramadol and control group. But no

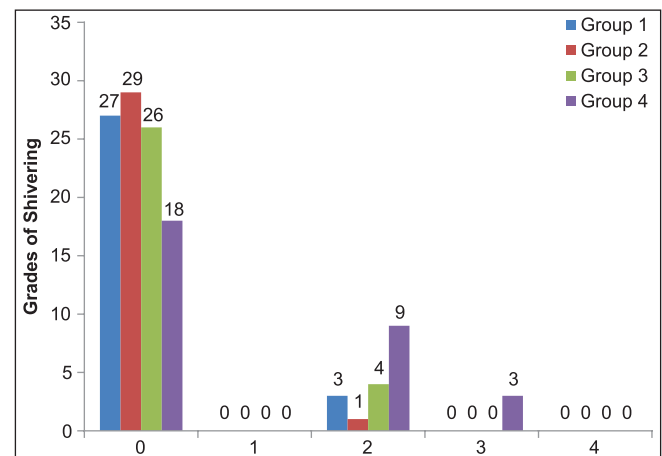


Figure 1: Grades of shivering observed in various groups

Table 1: Mean duration of surgery of subjects

| Group   | Mean duration of surgery (min) | SD   |
|---------|--------------------------------|------|
| Group 1 | 69.3                           | 22.0 |
| Group 2 | 73.7                           | 29.6 |
| Group 3 | 74.0                           | 22.5 |
| Group 4 | 72.7                           | 17.6 |
| P       | 0.9                            |      |

SD = Standard deviation

Table 2: Relationship of core temperature and shivering on admission to recovery room

|   | Group 1 (n = 30)  |                  | Group 2 (n = 30)  |                  | Group 3 (n = 30)  |                  | Group 4 (n = 30)  |                  |
|---|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|
|   | Shivering present | Shivering absent | Shivering present | Shivering absent | Shivering present | Shivering absent | Shivering present | Shivering absent |
| Mean tympanic membrane temperature (°F) | 96.6±0.4          | 96.6±0.4         | 96.5±0.0          | 96.5±0.4         | 96.6±0.4          | 96.6±0.4         | 96±0.4            | 96.6±0.4         |
| P                                       | 0.234             |                  | 0.245             |                  | 0.322             |                  | 0.329             |                  |

NS = Nonsignificant

**Table 3: Analgesic requirements**

|   | <b>Group 1<br/>(n = 30)</b> | <b>Group 2<br/>(n = 30)</b> | <b>Group 3<br/>(n = 30)</b> | <b>Group 4<br/>(n = 30)</b> |
|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patients requiring rescue analgesia (%) | 10 (33.3)                   | 4 (13.3)                    | 9 (30)                      | 18 (60)                     |

statistically significant difference was observed between patients who received clonidine and dexmedetomidine at 0 and 10 min.

Number of patients complaining of nausea were maximal in Group 2 where 7 patients (23.3%) out of 30 had nausea. Whereas only two patients (6.7%) out of 30 complained of nausea in Group 1, 3, and 4 each. Furthermore, the Grade 3 nausea requiring treatment was seen only in this group.

Mean VAS scores at all time intervals among all groups were statistically significant from 0 to 60 min and at 210 and 240 min. The time of admission to the recovery room (0 min) until 30 min, pain scores in patients of Group 4 were significantly higher than patients of Group 1, 2, and 3. VAS scores of patients who received clonidine (Group 1) were significantly higher than Group 2 and 3 at 20, 30, 210, and 240 min.

The number of patients requiring rescue analgesia was significantly less in tramadol group 2 (13%) as compared to Groups 1, 3 and 4. *P* value 0.008 [Table 3]. Patients in Group 1 required analgesia at  $38 \pm 19.2$  min, Group 2 at  $97.5 \pm 15$  min, Group 3 at  $42.2 \pm 17.2$  min and Group 4 at  $5.6 \pm 9.2$  min. These differences were found to be statistically significant (*P* value of 0.0001). Group 1, 2, and 3 had significantly longer time for rescue analgesia as compared to Group 4. Group 2 also significantly longer analgesic effect as compared to Groups 1, 3, and 4. However, no significant difference was found between the time to rescue analgesia of Group 1 and 3.

## Discussion

The incidence of shivering was least in the tramadol group followed by clonidine and dexmedetomidine. The incidence of shivering in the patients receiving clonidine in our study is similar to that in Delaunay *et al.*<sup>[8]</sup> and Horn *et al.*<sup>[9]</sup>, especially at higher doses (3 microgm/kg).

Bicer *et al.*<sup>[10]</sup> observed a 15% incidence of shivering with dexmedetomidine and 55% with placebo,<sup>[11]</sup> which is comparable to our observations. Elvan *et al.*<sup>[3]</sup> found that a loading dose of dexmedetomidine followed by maintenance infusion, reduced the incidence of shivering to 17.5% as compared to 52.5% with placebo.

Tramadol was shown by Trevoka *et al.*<sup>[12]</sup> to be more effective than the placebo. Mathews *et al.*<sup>[13]</sup> observed a reduction in the

incidence of shivering to 4% in the tramadol group as compared to 48% in control group, which is similar to our study findings. Saha *et al.* observed that tramadol administered at the time of wound closure decreased the incidence of shivering to 20% as compared to 60% in control group. Mohta *et al.*<sup>[14]</sup> compared the efficacy of tramadol in different doses of 1, 2 and 3 mg/kg with pethidine (0.5 mg/kg) and observed a reduction in the incidence of shivering (9%, 6%, 3%, and 12%, respectively), compared to that in the control group (42%).

Bhukal *et al.*<sup>[15]</sup> concluded that prophylactic pre-induction use of low dose pethidine does not have major role in preventing postoperative shivering. Furthermore Zahedi<sup>[16]</sup> observed superiority of tramadol to pethidine in preventing shivering, due to its earlier onset of action, less untoward consequences and its higher safety when used as an analgesic in the hands of nonanesthetics. Bhatnagar *et al.*<sup>[17]</sup> found that shivering was significantly more likely to have ceased in the tramadol group (12 of 15 vs. 4 of 15 cases, *P* < 0.05) at 10 min after drug administration and this control was better sustained. No patients receiving tramadol had a recurrence of shivering.

Tramadol, a nonopioid analgesic, inhibits postanesthetic shivering, lowers the thermoregulatory set point, doubles the inter threshold range and reduces the vasoconstriction and shivering threshold at doses of 1 mg/kg.<sup>[12]</sup> Clonidine reduces the threshold for shivering and vasoconstriction, and when given at induction reduces postanaesthetic shivering without influencing the core and peripheral body temperature distribution. Dexmedetomidine also reduces the incidence of shivering by the same mechanism,<sup>[2]</sup> though it is 8-10 times more specific for  $\alpha_2$  receptors than clonidine.

We found that all the three study drugs provide prophylaxis against shivering compared to placebo. However tramadol offered maximum efficacy in the prevention of shivering. Though tramadol was associated with higher incidence of nausea compared to clonidine, dexmedetomidine, and placebo, it was mild requiring no treatment in the majority of the patients. Clonidine caused significant postoperative sedation while patients who received tramadol and dexmedetomidine were not sedated compared to clonidine. All the three drugs provided postoperative analgesia with tramadol exhibiting maximum analgesic efficacy. There was no difference in analgesic efficacies of clonidine and dexmedetomidine. Thus, tramadol was found to be the most suitable agent in preventing postanesthesia shivering with the additional benefit of longer analgesic effect and least side effects.

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Nil.



## Conflicts of interest

There are no conflicts of interest.

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## 2016\_SGPGI

Our group at the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), Lucknow has been organizing workshops since 2010 on various aspects of clinical research, as part of an Indo-US collaboration. In continuation of the series, two workshops are planned in 2016 at SGPGI, Lucknow as follows:

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- Workshop on 'Basic Biostatistics', 26-28 August 2016.

These workshops are meant for active biomedical researchers who hold faculty positions and are poised to lead or are leading clinical research studies. These interactive workshops will have both didactic and practical sessions. Around 30 applicants will be considered for each workshop.

Those interested in attending the workshop(s) should fill the application form (which asks for a summary of experience and expertise in clinical research; available at <https://sites.google.com/site/spgpgimsnihcourses/>) and send it as an email attachment to [sgpgi\\_courses@gmail.com](mailto:sgpgi_courses@gmail.com). The last dates for applications for the above courses are 20 March 2016 and 30 June 2016, respectively. A selection committee will screen the applications and notify successful participants about 5 weeks in advance of each course.

The National Institutes of Health, USA provides funds to partially support the costs of course material and venue for the conduct of these workshops. The registration fee is Rs 5000 for participants who require accommodation (includes twin-shared guest house accommodation and all meals on all days). Those who will arrange their own accommodation will need to pay a registration fee of Rs 2000. Participants are expected to pay (by electronic bank transfer) the registration fee soon after intimation of selection.

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